REMARKS

Reconsideration of the instant application is respectfully requested in view of the remarks below. No claims are amended, and therefore, no new matter is introduced with this response.

The Examiner rejected the claims of the instant application as allegedly obvious in view of Tyagi (2000), Tyagi (1998), and Lee.

Specifically, the Examiner asserts Lee discloses hairpin probes comprising respective stems which dissociate if the reaction mixture reaches a certain temperature. The Examiner further asserts that it would be obvious at the time of the invention to include these hairpin probes into the distributed arrays disclosed in Tyagi (1998) and/or Tyagi (2000). Applicants respectfully traverse.

1. Instant invention

It appears that the previous responses to office actions did not sufficiently clarify the arrays of the instant invention. In this section, Applicants will explain the instantly claimed arrays with particular emphasis on the related aspects of coding scheme and the principle of operation of the arrays.

The basic idea of a distributed array is to first make a plurality of sets of microcarriers, e.g., beads, where every bead within a particular set of beads carries the same identifying code, and each bead in that set also carries a probe for a particular target (the intended target is usually a particular nucleic acid, such an mRNA, and the probe is usually a complementary nucleic acid that is often referred to as a "capture probe"). In other words, the same identifying code is always associated with the same particular target.

The instant invention concerns how each set of beads is encoded, so that beads that are members of a particular set can be identified, thereby providing the information needed to know which probe was attached to the beads in that particular set.

The coding scheme of this invention is the use of several kinds of signaling hairpins. The coding elements include not only fluorophore labels but also opening (and thus, unquenching) at different environmental conditions, such as at different temperatures. For example, a combination of three stem lengths (which will melt apart at different temperatures) and five differently colored fluorophores yields 15 different types of signaling hairpins (5 x 3).

To encode each particular set of beads, the practitioner decides for each of the 15 types of signaling hairpins, whether to covalently link thousands of molecules of that particular signaling hairpin (i.e. containing identical stem sequence and fluorophore) onto the surface of the beads in that particular set of beads, or not to covalently link any molecules of that particular signaling hairpin to the surfaces of that particular set of beads.

So, to encode a particular set of beads, 15 decisions are to be made (that is, for each of the 15 different signaling hairpins, one needs to decide if it will be present on the surface of the beads, or whether it will not be present on the surface of the beads). For each type of signaling hairpin, a binary decision is made: present or not present. Thus, for each bead, 15 decisions are made. There are thus 2 raised to the power 15 different codes to choose from (2 raised to the power 15 equals 32,768). Thus, with only five different fluorophores and three stem lengths, one has a code of 32,768 elements.

The key thing in this approach is that among these thousands of sets of beads, each individual set of beads has a distinguishable code determined by which signaling hairpins are covalently linked to its surface. These differently coded bead sets can be manufactured in bulk, stored, and the same stock preparations can be used for many years by a manufacturer of distributed arrays.

Once the practitioner decides that he wants to access the expression of, for example, 1670 different mRNAs, the practitioner would obtain 1670 different sets of beads, as described above, and 1670 different hybridization probes, each probe specific for one mRNA. The practitioner then would link each hybridization probe (actually, billions of identical hybridization probes) to a single set of the already coded microbeads (i.e., microbeads having identical codes). As a result, each uniquely coded set of microbeads would be associated with a single kind of hybridization probe. The next step is to mix together all 1670 types of beads, each of which possesses one type of hybridization probe on its surface.

The beads are then mixed with the sample containing the mRNAs to be analyzed. At this point, the relevant reaction is binding of the hybridization probe to the mRNAs in the sample. One of these molecules, either the target or the capture probe, can be labeled, e.g., with a fluorophore. Which molecule (the mRNA target or the hybridization probe) is labeled is immaterial. The important aspect is that the binding must be registered, so as to distinguish beads bound to targets from beads that are not bound to targets. In the scenario above, light

emission would be sufficient. The intensity of the fluorescence on the surface of those beads will depend on the abundance of the matching mRNA in the sample being analyzed. This is the first step in the assay.

There are many different mechanical formats in which the resulting "hybridized beads" can be analyzed. For the purposes of illustration, in one format, all of the beads in the mixture (say 25000 beads) are packed together on the surface of a microscope slide. The beads are usually quite small, and 25000 beads can fit on the surface of a microscope slide - that is why they are often called "microbeads" or "microcarriers". Once they are laid out in this manner, they are immobilized – that is, they can no longer move about. The microscope slide containing the beads is then placed on the stage of a scanning fluorescence microscope, and the stage is maintained at the same temperature at which the hybridization was carried out. Under the control of the computer, the image is rapidly scanned, and the fluorescence intensity of each bead is recorded.

The decoding process then takes place. The temperature of the microscope stage is slowly increased (which results in an increase in the temperature of the solution surrounding the beads). At some point, the temperature is sufficiently high that the target mRNAs dissociate from the capture probes (if the capture probes are molecular beacons, the departure of the unlabeled mRNAs causes the molecular beacons to become non-fluorescent – if the capture probes are conventional linear oligonucleotides, the departure of the labeled mRNAs results in the marked lowering of fluorescence on the surface of the beads, as the released labeled mRNAs are dispersed throughout the slide – in either case, the beads become dark). So, at this stage in the process, the computer has recorded the fluorescence intensity of every individual bead to which mRNAs were bound, but the computer does not know which of the immobilized beads is which – that is, the computer does not know the identity of the mRNA that was captured by each of the beads that was rendered fluorescent. By this time it is known which beads have captured target molecules.

The next step is to determine which bead is which. The following process reflects the gist of the instant invention.

As the dark beads are heated further, a first temperature is reached at which the signaling hairpins with the shortest stem length change their shape from a hairpin to a random coil. In the

random coil configuration, the fluorophores at one end of the short signaling hairpins are no longer in close proximity to the quencher groups at the opposite end.

Consequently, these short signaling hairpins become fluorescent, emitting the characteristic color of the fluorophore attached to their ends. The images from the microscope are continuously analyzed and recorded, e.g., in a computer, thus registering the fluorescent colors emitted by each bead. Some beads will not fluoresce at all at this first temperature (and the computer will note that); some will fluoresce in one of the five colors (and the computer will note which color that is); others will fluoresce in two out of the five colors (and the computer will note which two colors those are); some will fluoresce in three colors (and the computer will note which three colors those are); some will fluoresce in four colors (and the computer will note which four colors those are); and some will fluoresce in all five colors (and the computer will note that).

Thus, the computer will register 32 events: lack of fluorescence plus 31 different instances of fluorescence, illustrated as follows:

Assuming that fluorophores are designated a, b, c, d, e, the combinations are:

A) single colors: a, b, c, d, e: 5 combinations;

B) two colors: ab, ac, ad, ae, bc, bd, be, cd, ce, de: 10 combinations;

C) three colors: abc, abd, abe, acd, ace, ade, bcd, bce, bde, cde: 10 combinations;

D) four colors: bcde, acde, abde, abce, abcd: 5 combinations;

E) five colors: abcde: 1 combination;

F) no colors: 1 combination

Overall: 32 combinations.

The analysis continues as the temperature is increased further until the point is reached where signaling hairpins having stems of the intermediate length open up. The computer notes for each bead which new colors have arisen on each bead (and the computer even notes if a color that arose on a bead as a result of a short signaling hairpin opening up now has double intensity, indicating that an intermediate length hairpin labeled in the same color has also opened up). The same 32 events are registered at a second temperature. The information gathered through this point yields 32^2, or 1024 combinations.

Finally, the temperature of the slide is raised so high that the signaling hairpins with the strongest hybridization reveal their presence (or their absence) on each bead immobilized on the

slide, thus producing another 32 events. The information gathered at this point yields 1024 x 32 = 32,768 combinations.

Notably, it is desirable to raise the temperature to a degree which is significantly greater than the highest melting temperature of the signaling hairpin stems. See, e.g., specification as published, paragraph 0015 ("If, for example, the signaling hairpins are constructed to melt at 58, 72 and 82 °C, and the analyte hybridization is carried out at 50 °C, the temperature of the slide can be raised to 88 °C at a rate suitable for the instrumentation, such as a few degrees a minute, and real-time fluorescence curves can be obtained for each bead.")

After the 25,000 or so beads on the slide are scanned during the increase of temperature of the slide, the code associated with each individual bead becomes known (i.e., for every bead on the slide there is a list of which colors appeared at the lowest signaling hairpin stem melting temperature, which colors appeared at the intermediate melting temperature, and which colors appeared at the highest melting temperature). The code of each bead is then compared by the computer to a table that relates each code to the identity of the capture probe that is immobilized on the surface of that bead. Consequently, the computer is then able to determine the identity and quantity of the target mRNA that was hybridized to each bead. Since the fluorescence intensity of each bead was determined by detecting the fluorescence of the hybrid formed by the binding of the target mRNA to the capture probe at the hybridization temperature (which is lower than the temperatures used to subsequently decode the beads), a quantitative measure of the amount of target mRNA that hybridized to each bead is also known. As a last step, the recorded intensities of all of the beads that came from the same set (i.e., that have the same code) are added up and divided by the number of beads that possess that same code. This averaging of the results from approximately 15 different beads possessing the same code (approximately 25,000/1,670 beads of each type) gives a very accurate measure of the abundance of each of the 1,670 different mRNAs in the sample.

2. Analysis of references cited by the Examiner

Tyagi, *Nature Biotechnology* 18:597-598 (2000) ("Tyagi" or "Tyagi 2000"), is a review of a paper by Brenner et al. in the same issue of the journal. The review consists of two parts. The first part is an explanation of, and comment on, the Brenner et al. paper's method. The second part, beginning with the last paragraph in the middle column on page 598, is a comment

on other methods that also have used non-positional microarrays, that is, distributed arrays in which position does not identify a particular microbead or what capture probe it carries.

The method of the Brenner et al. paper is to attach a different 32-mer capture oligonucleotide (actually about 100,000 copies) to each microbead. Part of each 32-mer is the complement of an address tag that is 16-20 nucleotides long. Thousands of these labeled beads are then assembled as a library. To this library are exposed conjugates of target and address tag that have been made by cloning and then amplified by PCR using one primer that is labeled with a fluorophore. The address tag of a target conjugate will hybridize to its complement in a bead's capture probe. Each bead will capture copies of only one target, but the question remains, "What is the sequence of the target captured by that bead?" Brenner et al. do not deduce the target sequence by interrogating the bead for the identity of its address-tag complement, Rather, Brenner et al. sequence all the captured targets in parallel by a novel method, described on page 598 in the paragraph bridging columns 1 and 2. First the beads are immobilized on a planar surface. Then all target sequences are sequenced by a series of five cycles, depicted in Figure 2, reproduced below.

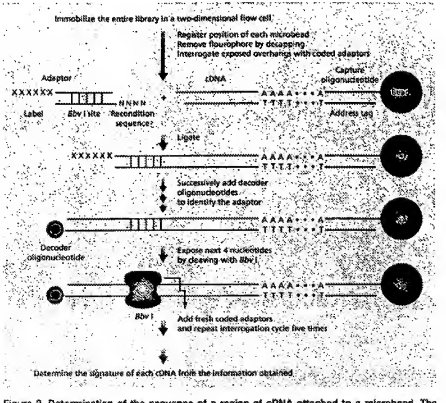

Figure 2. Determination of the sequence of a region of cDNA attached to a microbead. The process is illustrated for one microbead, although it is performed on the entire library in parallel.

Each cycle includes adding and ligating an adapter oligonucleotide, adding a fluorescently labeled decoder oligonucleotide that hybridizes to the adapter and four terminal nucleotides of the adjacent target sequence, causing the bead to fluoresce if the decoder oligonucleotide binds. Between cycles the target is shortened so that the next cycle will see if a particular decoder oligonucleotide binds to adapter plus the next four nucleotides of the target sequence. Hundreds of thousands of mRNAs can be sequenced in parallel by this method in only a few days.

The second part of Tyagi's review notes that the Brenner et al. method falls into the general category of distributed arrays. Tyagi refers to and cites other distributed-array methods, including methods utilizing beads containing optical barcodes made by "imbibing" beads with unique combinations of differently colored fluorescent dyes. This approach has been dealt with previously during prosecution of this application – the reference was Spiro et al. Tyagi cites other references, e.g., Iannone, M.A. et al. *Cytochemistry* 39:131-140 (2000). Iannone et al. discloses covalently immobilizing on each of 58 bead types an oligonucleotide containing a sequence complementary to a capture probe; preparing 58 capture probes, each including the sequence complementary to a bead sequence and also a capture sequence complementary to a SNP region of one of the 58 targets; and preparing target-complementary fluorescently labeled reporter probes that would hybridize to targets adjacent to the capture sequence of the capture probe, where they could be ligated to, and thereby add a label to, a capture probe by the known oligonucleotide ligation assay technique. Upon mixing target solution with the foregoing reagents, certain beads would become fluorescent, indicating the presence of a particular target. To determine which target, Iannone et al. utilized Luminex Corp. beads impregnated with red and orange dyes in various ratios – the same coding system as the Spiro et al. reference, which was previously relied on by the Examiner, dealt with, and ultimately overcome by Applicants.

Lee does not disclose or discuss coding or multiplexing. Lee teaches molecular probes to monitor the temperature in PCR reactions for use in place of instrumental probes (such as thermometers). The temperature probes are double-stranded oligonucleotides or single-stranded oligonucleotides having a double-stranded region, such that melting affects fluorescence. One temperature probe, depicted in Fig. 2, is a hairpin oligonucleotide terminally labeled with a

FRET pair. The hairpin is designed such that its stem melts at the PCR annealing temperature, although one or two more probes can be added to monitor also the PCR extension and/or denaturation temperatures (page 5, lines 30-37).

Tyagi et al. (1998) ("Tyagi 1998") reference describes the use of molecular beacon probes for allele discrimination. It describes, among other things, addition of four differently colored allele-discriminating molecular beacons to four tubes, each containing one of four different allelic targets. As shown in Figure 5, only the perfectly matched molecular beacon fluoresces.

3. Analysis of the Examiner's argument

Applicants respectfully submit that the rejection confuses two distinct parts of Tyagi's review. The first part of the review is an analysis of an assay of Brenner et al. that is generally shown in Figures 1 and 2. Finding this assay to be an example of an assay that does not use a positionally encoded array, the second part, comprising the final two paragraphs in columns 2 and 3 on page 598, reports other assays previously known that also do not utilize positional arrays, such as the barcode techniques of references dealt with earlier in the prosecution of the instant application, most notably Spiro et al. As Spiro et al. had not yet been published, Dr. Tyagi cites Iannone et al. (2000) *Cytochemistry* 39:131-140 (2000) for barcoding. It discloses the identical barcoding used by Spiro et al., that is, microbeads from Luminex that are impregnated with red and orange dyes in various ratios:

> Polystyrene microspheres (5.5 μm in diameter) with a carboxylated surface and different ratios of red and orange fluorescence were purchased from Luminex Corp. (Austin, TX). (Iannone et al., page 132).

The reason it is critical to appreciate the two different parts of Tyagi 2000 is that the new Brenner et al. assay depicted in Figures 1 and 2 rejects decoding microbeads and opts instead for sequencing the captured targets themselves. The new assay is not a variant of coding/decoding microspheres. The two parts of Tyagi 2000 are not combinable.

Turning to the specifics of the application of Tyagi (2000) to claim 17, the rejection cites that the new Brenner et al. assay of Figures 1 and 2 is a hybridization assay for at least one (the assay is actually for thousands) of a multiplicity of nucleic acid sequences in which target sequences are captured by capture probes on microbeads. The rejection then ignores the remainder of the assay, shown in Figure 2 and described in the paragraph bridging columns 1

and 2 on page 598. In the assay, the unique 32-mer oligonucleotides on each microbead are not detected to infer what target sequence has been captured.

Instead, in this assay captured targets are sequenced in a massively parallel sequencing method that includes immobilizing the beads into a fixed 2-dimensional array, serially exposing the first 20 nucleotides of the targets four nucleotides at a time, and using labeled probes (called "decoder oligonucleotides") to identify the four exposed target nucleotides before cutting them off with a restriction enzyme that exposes the next four target nucleotides, which are then identified using labeled decoder oligonucleotides, and so on, until 20 target nucleotides are identified. It will be appreciated that for this sequencing scheme to work, each bead must have a fixed location in order to know which 4-nucleotide sequences match to the same target sequence, and the target sequence must stay attached to the microbead for the full length of the decoding step. The sequencing operation can be completed "in only a few days."

At best, the direct detection of these 32-mers (referred to as capture probes in Tyagi 2000) would require significant redesign of Brenner et al's. assay based on nothing but an improper hindsight, and at worst, would be useless. Since these 32-mer oligonucleotides form a stable double-stranded structure and each nucleotide in each 32-mer oligonucleotide is paired up with a unique address tag attached to the target (see Fig. 2 above), the specific detection of each such 32-mer oligonucleotide would involve de-hybridization of this 32-mer and the corresponding address tag, which would result in the target leaving the microbead. Considering that in Brenner et al.'s system it is unknown which 32-mer oligonucleotide corresponds to which mRNA, identification of each 32-mer would be pointless.

In place of the new Brenner et al. assay, the rejection substitutes the barcoding technique discussed in the second part of Tyagi 2000. But barcoding cannot be combined with the new assay, because the new assay eschews – teaches away from – decoding beads, in favor of directly sequencing captured targets. To rely on the second part of Tyagi 2000 is simply to restate the previous rejection based on Spiro et al., which rejection has been withdrawn. Applicant requests that the new rejection be withdrawn for that reason.

The additional references, Lee, and Tyagi et al. (1998) do not teach coding/decoding microbeads using a plurality of signaling hairpins of different colors. It certainly was known from molecular beacon probes that hairpin oligonucleotides have characteristic melting temperatures based on their structure, including, for example, stem length and composition. See,

for example, Fig. 6 of Tyagi et al. 1998, which presents a thermal denaturation curve for a particular molecular beacon probe. And it was known that molecular beacon probes having different loops (target recognition sequences) could be differently labeled, as shown in Tyagi et al. (1998). Lee teaches construction of hairpins having melting temperatures matching the annealing, extension, and/or denaturation temperatures of a PCR reaction for use as free-floating temperature probes to monitor the PCR reaction – to make sure the actual annealing, extension, and/or denaturation temperatures are the intended annealing, extension, and/or denaturation temperatures without the need for an instrumental temperature probe. Using hairpins in solution for temperature monitoring during PCR is in no way related to decoding microbeads by melt analysis of a combination of hairpins immobilized on individual beads. There is no teaching or suggestion in Lee to use hairpins to code microbeads; there is no suggestion to immobilize hairpins on beads for any purpose; there is no suggestion to decode individual microbeads by changing temperature or any other environmental condition to see what combination of hairpins a particular microbead has on its surface. Similarly, Tyagi et al. (1998) contains no suggestion to code individual microbeads with a combination of hairpins that signal at different temperatures. The only way to combine any two of the three cited references is by hindsight using Applicant's invention as a guide, and that does not create a case of prima facie obviousness.

Applicants further note that in the Brenner et al. assay described in Tyagi, 2000 the target participates directly in the identification step. This principle of operation is in direct contrast to the instant assay, where the target may completely leave the probe after the detection step and during the decoding, without affecting the accuracy of the assay!

Thus, if Tyagi 2000 is modified as suggested by the Examiner, the resulting array system would significantly change the principle of operation of Tyagi. This is improper under MPEP § 2143.01.VI, which states that the proposed modification cannot change the principle of operation of the prior art. Applicants further respectfully note that MPEP § 2143.01.VI necessarily suggests that it is proper and, in this case, crucial to analyze the mechanism of action of the probes disclosed in the prior art. Accordingly, proper analysis of the operation principles of the assays claimed herein and assays disclosed in the prior art is respectfully requested.

Now, turning to Lee, Applicants note that Lee's hairpins are not fixed, they are present in a free-floating form. As noted above, there is no motivation to place these hairpins onto microbeads. Further, the hairpins of Lee are not used to decode anything, but only to determine

whether a particular temperature has been reached in an enzymatic reaction. Lee specifically teaches that his invention (i.e., adding the hairpins into the reaction mixture) serves as an indicator of whether a particular temperature has been reached in a system, without the need to provide an external instrumental probe.

A crucial distinction between the instant claims and the disclosure of Lee is decoding: in the instant invention, target detection and bead decoding are distinct steps, and bead decoding is performed after target detection, and bead decoding is the step in which the temperature is increased. In Lee, there is no decoding during the increase in temperature, only an indication of when a particular temperature is reached. Lee contains no suggestion of using hairpins as coding elements.

The Examiner further writes that "one of ordinary skill in the art is motivated to use molecular beacons taught by Tyagi 1998 labeled with different fluorophore and quencher pairs as capture probes in the microbead system taught by Tyagi 2000 with a reasonable expectation of success in being able to perform qualitative real time detection of multiple targets simultaneously." Office Action at 15, emphasis added. The salient point is that this subject is irrelevant. The invention claimed in this application is about signaling hairpins , not about capture probes. If Lee, Tyagi 1998, and Tyagi 2000 were combined, one would have only differently colored capture probes immobilized on beads. Clearly, this is not even close to the instantly claimed system.

The term "capture probes," used previously, refers to presently recited hybridization probes, which are exactly that: probes which hybridize to targets. At best, considering that the maximal number of fluorophores which could be used without significant spectral overlap is about eight, there could be eight indicators of hybridization. Since only a single species of a hybridization probe is used on each microbead, the number of distinguishable probe-target binding events is eight, contrary to the Examiner's assertion of "100s to 1000s targets." See page 16. Further, in the system proposed by the Examiner, the probes for detection and the probes for decoding are identical, which is in contrast to claim 17. This deficiency has been noted in paragraph 0004 of the instant application as published.

The Examiner goes on to state that in her proposed system (see above), Lee's temperature probes are incorporated to monitor the progress of the reaction. That is not the function of Applicants' signaling hairpins. Moreover, Applicants respectfully ask, which reaction?

Apparently, the Examiner refers to the hybridization reaction, since the conditions of the decoding step are monitored by other means (e.g., an instrumental temperature sensor, which Lee eschews), or the conditions (e.g., temperature) are pre-selected to such a degree that the desired condition will occur. In addition, the use of Lee's temperature probes in a step other than the hybridization reaction would ruin the principle of operation and the operability of Lee. According to MPEP § 2143.01.V, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." As noted above, the coding scheme of the instant array is not involved in a hybridization reaction at all, and preferably, the coding hairpins are not disrupted during hybridization.

Further, the Examiner presents an incorrect mathematical analysis of possible coding combinations offered by Lee. She proposes that Lee discloses 3^n to 8^n fluorophore-hairpin combinations, where n is the number of spectrally distinguishable fluorophores. That is incorrect. Lee discloses using only one, two or three hairpins. The use of these three hairpins together with n spectrally distinguishable fluorophores provides only 3n hairpin-fluorophore combinations, rather than 3^n. As noted above, the number of spectrally distinguishable fluorophores is about eight. Thus, Lee discloses only about 24 fluorophore-hairpin combinations. Thus, the mathematical analysis provided by the Examiner is incorrect. Applicants further respectfully note that in Lee's system, the use of these 24 fluorophore-hairpin combinations does not provide any greater information than the use of 3 fluorophore-hairpin combinations because in Lee's system the hairpins are present in a free-floating form in a solution.

The crucial step, not suggested by any of the references and eschewed by Tyagi 2000 is immobilizing combinations of signaling hairpins onto the microbeads (see claim 17: "mixture of encoded microcarriers having immobilized on their surfaces … a coding scheme comprising a plurality of signaling hairpins that are not hybridization probes for said multiplicity of sequences"). The placement of signaling hairpins onto microbeads involves a binary "yes" or "no" decision, as to whether, for example, to place each of 15 hairpins (three different lengths, five differently colored fluorophores) on a particular microbead, resulting in the number of combinations being 2^{15} (i.e., 32,768 different codes).

The fact that the Examiner did not realize this advantage, as demonstrated by the flawed mathematical analysis, combined with the legal principle that the Examiner should put him- or herself into the shoes of a person of ordinary skill in the art (MPEP § 2142, *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) stating that the examiner must "step … into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown"), demonstrates that such an increase in the number of coding combinations (i.e., via placing hairpins onto microbeads) is not obvious.

The other references, namely, Walt (*Science* 287: 451-452 (2000)) and Frutos (US 6,579,680) do not solve the deficiencies of the combination of Tyagi 2000, Tyagi 1998, and Lee, as discussed above.

For at least these reasons, independent claim 17 is not obvious in view of the references cited by the Examiner. Since claim 17 is not obvious, all claims dependent therefrom (in this case, all other claims in this application) are also not obvious.

Accordingly, Applicants respectfully request the Examiner to withdraw the instant ground for rejection.

CONCLUSION

Applicants respectfully submits that for at least these reasons the pending claims are valid and favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, Applicants request a personal meeting with the Examiner.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

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